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Influence of Hypertension, Lipometabolism Disorders, Obesity and Other Lifestyles on Spontaneous Intracerebral Hemorrhage

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Objective To investigate whether hypertension, abnormal lipometabolism, obesity, cigarette smoking and alcohol drinking affect the intracerebral hemorrhagic volumes (IHV) in patients with spontaneous intracerebral hemorrhage (SIHP), and to explore the roles of these factors in spontaneous intracerebral hemorrhage (SIH). **Methods** Five hundred patients with acute SIH and 200 healthy adult volunteers (HAV) were enrolled in a study of independently randomized controlled design, in which the levels of systolic pressure (SP) and diastolic pressure (DP), and total cholesterol (TCH), triacylglycerols (triglycerides, TG), high density lipoprotein cholesterol (HDL-CH), low density lipoprotein cholesterol (LDL-CH) in serum as well as the level of erythrocytic membrane cholesterol (EM-CH) were measured, and the body mass index (BMI), daily cigarette smoking consumption (DCSC) and daily pure alcohol consumption (DPAC) were calculated. **Results** Compared with the average parameters in the HAV group, those of SP, DP, TG, LDL-CH and BMI in the SIHP group were significantly increased ($P<0.0001$), while those of HDL-CH and EM-CH were significantly decreased ($P<0.0001$). The linear regression and correlation analysis showed that with increased SP, DP, LDL-CH, BMI, DCSC, DPAC and aging as well as decreased HDL-CH and EM-CH, the IHV levels in SIHP were increased gradually ($P<0.0001$-0.01). The linear stepwise regression analysis suggested that there existed a close correlation among the values of SP, DP, TCH, TG, HDL-CH, LDL-CH, EM-CH, BMI, DCSC, DPAC, age and IHV of the SIH patients, and that $Y = -12.4583 + 0.1127SP - 1.1977EM\text{-}CH + 0.9788LDL\text{-}CH + 0.2477BMI + 0.0382DCSC + 0.0248DP$, $P<0.0001\sim 0.05$. **Conclusions** The findings in the present study suggest that significantly increased systolic and diastolic pressure, low density lipoprotein cholesterol, body mass index and daily cigarette smoking consumption, and significantly decreased erythrocytic membrane cholesterol may be likely the main factors affecting intracerebral hemorrhagic volumes in patients with acute spontaneous intracerebral hemorrhage.

Key words: Blood pressure; Lipids; Cigarette smoking; Alcohol drinking; Body mass index; Spontaneous intracerebral hemorrhage; Intracerebral hemorrhagic volume

INTRODUCTION

Cerebral hemorrhagic stroke (CHS) is a clinical syndrome characterized by the sudden

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onset of a focal neurologic deficit persisting for at least 24 h and is due to abnormal cerebral circulation. CHS is one of the leading causes of death in China. CHS can be divided into intraparenchymal hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage, hemorrhage caused by iatrogenic anticoagulation, hemorrhage due to vascular malformations and hemorrhagic ischemic infarction, etc.[1-4]. Significant risk factors mainly include hypertension[1-13], hypercholesterolemia[1-4,10,11,13-17], diabetes[1-4,18], smoking[1-4,8,10,11,18-20], heavy alcohol consumption[1-4,8,13,18-22], oral contraceptive use[1-4], amyloid angiopathy[1-4,23], aging[1-4], obesity[1-4,19,20,22,24] and others. These risk factors are also associated with low intake of saturated and unsaturated fat, and animal protein[25], low serum total cholesterol[25-27] and low erythrocyte membrane cholesterol[28]. However, up to now, there have been neither reports on the factors affecting spontaneous intracerebral hemorrhage (SIH), nor reports about the relationship between SIH and blood pressure, lipometabolism, body mass index (BMI), cigarette smoking and alcohol consumption. To investigate whether the changes of these factors affect intracerebral hemorrhagic volumes (IHV) in SIH patients, and to explore the roles of these factors in SIH, 500 SIH patients (SIHP) and 200 healthy adult volunteers (HAV) were enrolled in a study of independently randomized controlled design, in which the levels of systolic pressure (SP) and diastolic pressure (DP), and total cholesterol (TCH), triacylglycerols (TG), high density lipoprotein cholesterol (HDL-CH) and low density lipoprotein cholesterol (LDL-CH) in serum, and erythrocytic membrane cholesterol (EM-CH) were determined, and BMI, daily cigarette smoking consumption (DCSC) and daily pure alcohol consumption (DPAC) were calculated. Additionally, differences between the average parameters in the SIHP group and the HAV group were compared, and linear regression and correlation analysis, partial correlation analysis, and linear stepwise regression analysis were conducted.

MATERIALS AND METHODS

Study Design

A randomly controlled design was used in the present study. In order to obtain an objective research conclusion, principles of random sampling, control, replication and equilibrium, and management factors, experimental effects, and inclusion and exclusion criteria of the subjects were all taken into full consideration, and strictly executed in the study[28-30].

Subjects

SIHP. Five hundred SIH patients (278 males and 222 females) in acute phase were randomly sampled from 759 SIH patients according to the inclusion and exclusion criteria[1-4] with "Select Cases-Random Sample" of "SPSS 11.0 for Windows". Their diagnoses were confirmed by CT and/or MRI, and their ages ranged from 48 to 72 (59.9 ± 5.3) years. Their IHV was from 1.32 to 25.83 mL (8.59 ± 5.36). In the above patients, those with subarachnoid hemorrhage, hemorrhage due to cerebrovascular malformations, amyloidosis (amyloid angiopathy) and brain trauma (traumatic cerebral hemorrhage), bleeding diathesis due to iatrogenic anticoagulation, cerebral thrombosis or cerebral embolism, and those with no-SIH or with hemorrhage due to other traumas were excluded[1-4]. All the patients were within normal ranges in their routine blood, urine and feces tests and radiographs, and marked disorders associated with heart, lung, liver, kidney and other organs were excluded, and diseases such as acute or chronic bronchitis, autoimmune disease, diabetes, cataract and

tumors were also excluded. They were volunteers in this study.

HAV. Two hundred HAVs (104 males and 96 females) were randomly sampled from 400 HAVs confirmed by comprehensive physical examination at the Second Affiliated Hospital, College of Medicine, Zhejiang University, with "Select Cases-Random Sample" of "SPSS 11.0 for Windows". Their ages ranged from 50 to 72 (60.6±8.9) years. All HAVs were within normal ranges in their routine blood, urine and feces tests, ECG and radiographs, and disorders associated with heart, brain, lung, liver, kidney and other organs were excluded, and diseases such as hypertension, hyperlipidemia, atherosclerosis, acute or chronic bronchitis, autoimmune disease, diabetes, cataract and tumors were excluded, and nutritional diseases like subnutrition, malnutrition, supernutrition and others were also excluded. In addition, the above HAVs all had no cigarette smoking and alcohol drinking history. They were volunteers in this study.

There was no significant difference between the age averages in the SIHP group and the HAV group by the independent-sample t test (t=0.9721, P=0.3319), and neither significant difference between the gender proportions in the two groups by the Pearson chi-square test (χ^2=0.7468, P=0.4016). There was no significant difference between annual earnings, education levels, professions or occupations as well as residence regions (city or countryside, plain or mountainous area) in the two groups.

The above subjects were exposed neither to radiation, nor to intoxicating materials or pesticides. Within the prior month before they volunteered for the study, none of them had taken any hypotensor-supplements such as ginkgo biloba, tea polyphenols or other similar substances.

Methods

Determination of Blood Pressures

The levels of SP and DP of each subject were determined with a desk model sphygmomanometer at 10 a.m. 3 times on the left brachial artery at heart level, and the average values of SP and DP were expressed as mmHg.

Collection and Pretreatment of the Blood Samples

Fasting venous blood samples were collected in the morning from all the subjects and sera were promptly separated, and heparin sodium was added as anticoagulant in the other fasting venous blood samples, and the promptly separated erythrocytes were stored at –50℃ immediately[29, 30]. The blood samples were free from any hemolysis.

Determination of TCH, TG, HDL-CH, LDL-CH Levels in Serum

The levels of TCH, TG, HDL-CH and LDL-CH in serum were determined by an automatic biochemistry analyzer, and expressed as mmol/L.

The analytic reagents used to determine the above biochemical substances were purchased from Japan, and the analytical instrument was OLYMPUS AU2700-Automatic Biochemistry Analyzer, Japan.

Determination of EM-CH Level

Isopropyl alcohol was used to sedimentate hemoglobin (Hb) from a hemolytic solution (HS) of erythrocytes without white blood cells and platelets, and EM-CH in erythrocytic

membranes was extracted in the HS. The Hb level in the HS was determined. Isopropyl alcohol, water and the extract solution containing EM-CH were vaporized in a water bath at 100℃. The remaining biochemical substance (EM-CH) was further used for the determination of plasma TCH level[28], with a wavelength of 500 nm and a cuvette pathlength of 1.0 cm. The EM-CH level was expressed as μmol/g.Hb.

The analytical reagents and the standard cholesterol used to determine EM-CH were purchased from Trace Scientific Baulkham Hills, N.S.W., Australia, and the analytical instrument was Hewlett Packard 8453-Spectrophotometer, USA.

Calculation of BMI

BMI=body weight (kg)/body height $(m)^2$.

Calculation of DCSC

Every SIH patient's daily cigarette smoking consumption was converted into the standardization according to the tar and nicotine levels in a cigarette[30], and the SIH patient's DCSC ranged from 0 to 40 (9.4 ± 10.8) cigarettes.

Calculation of DPAC

Each SIH patient's daily drinking dose was converted into the daily pure alcohol consumption (DPAC) by standardization treatment[29], and the SIH patient's DPAC ranged from 0 to 98 (25.8 ± 25.1) grams.

In determination of the above parameters, the standardization of experiment, e.g. the same batch number of each reagent, the same quality control, the same lab assistant, and the identical analytical apparatus were strictly used for each experiment in order to decrease errors, and to ensure the analytical quality of determinations[29,30].

Medical Statistical Analysis

All data were statistically analyzed with SPSS 11.0 for Windows using a Compaq Pentium Ⅳ/2.4 GHz computer. The parameters in this study presented normal distributions by Kolmogorov-Smirnov Z test, and were expressed as mean plus or minus standard deviation ($\bar{x} \pm s$) and 95 % confidence interval (95% CI). Hypothesis testing methods included the independent-samples t test, the Pearson chi-square test, the bivarate linear regression and Pearson product-moment correlation analysis, the partial correlation analysis, and the linear stepwise regression. In statistical analysis in this study, the level of hypothesis testing (α) was $\leqslant 0.05$ in order to avoid false positives (Type Ⅰ error), and the power of hypothesis testing (*power*) was $\geqslant 0.90$ to avoid false negatives (Type Ⅱ error)[29,30].

RESULTS

Comparison Between Parametric Averages ($\bar{x} \pm s$) in Groups of SIHP and HAV

Compared with the averages of parameters in the HAV group, the averages of SP, DP, TG, LDL-CH and BMI in the SIHP group were significantly increased, while those of HDL-CH and EM-CH in the SIHP group were significantly decreased (Table 1). The lower limits of 95% CI of the averages of SP, DP, TG, LDL-CH and BMI in the SIHP group were greater than the upper limits of 95 % CI of the same averages in the HAV group, and the upper limits of 95 % CI of HDL-CH and EM-CH in the SIHP group were less than the lower

limits of 95 % CI of the same averages in the HAV group (Table 1).

TABLE 1

Comparison Between Averages ($\bar{x} \pm s$) of Parameters in Groups of SIHP and HAV

Group	n	SP (mmHg)	DP (mmHg)	TCH (mmol/L)	TG (mmol/L)	HDL-CH (mmol/L)	LDL-CH (mmol/L)	EM-CH (nmol/g.Hb)	BMI
SIHP	500	170.9±23.8	100.2±15.5	4.48±0.78	1.80±1.12	0.94±0.45	4.14±1.04	10.32±1.26	29.30±2.66
		(168.8-173.0)	(98.8-101.6)	(4.41-4.54)	(1.70-1.90)	(0.90-0.98)	(4.05-4.23)	(10.21-10.43)	(29.06-29.53)
HAV	200	122.2±12.8	72.8±9.3	4.42±0.77	1.05±0.44	1.32±0.29	2.67±0.33	11.65±1.43	22.05±1.62
		(120.4-124.0)	(71.6-74.2)	(4.32-4.53)	(0.99-1.11)	(1.28-1.36)	(2.63-2.72)	(11.45-11.85)	(21.83-22.28)
t*		34.8903	28.6581	0.8009	12.5883	13.1780	28.2756	11.5159	43.8475
P		<0.0001	<0.0001	0.4234	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Note. * Independent-samples t test. The figures in parentheses are 95 % CI.

Linear Regression and Correlation Analysis between Each Parameter and IHV of SIH Patients

The findings of linear regression and correlation analysis between the values of SP, DP, TCH, TG, HDL-CH, LDL-CH, EM-CH, BMI, DCSC, DPAC, age and the IHV in the SIH patients showed that with increased SP, DP, LDL-CH, BMI, DCSC, DPAC and age as well as decreased HDL-CH and EM-CH, the IHV of the SIH patients were increased gradually (Table 2).

TABLE 2

Linear Regression and Correlation Analysis between the Each Parameter and IHV

Correlative Items	n	Regressive Equation	r	t	P
SP with IHV	500	Y = – 18.9870 + 0.1614 X	0.7160	22.8893	<0.0001
DP with IHV	500	Y = – 7.9792 + 0.1654 X	0.4780	12.1452	<0.0001
TCH with IHV	500	Y = 10.7759 – 0.5253 X	– 0.0710	1.5868	0.1132
TG with IHV	500	Y = 7.9041 + 0.3847 X	0.0808	1.8091	0.0710
HDL-CH with IHV	500	Y = 10.1526 – 1.6538 X	– 0.1390	3.1314	0.0018
LDL-CH with IHV	500	Y = 0.6438 + 1.9211 X	0.3720	8.9430	<0.0001
EM-CH with IHV	500	Y = 32.2692 – 2.2939 X	– 0.5411	14.3571	<0.0001
BMI with IHV	500	Y = – 3.8265 + 0.4240 X	0.2109	4.8155	<0.0001
DCSC with IHV	500	Y = 7.8420 + 0.0805 X	0.1618	3.6587	0.0003
DPAC with IHV	500	Y = 7.4353 + 0.0045 X	0.2104	4.8025	<0.0001
Age with IHV	500	Y = 1.5834 + 0.1170 X	0.1151	2.5848	0.0100

Note. Bivariate Linear Regression and Pearson Product-moment Correlation Analysis.

Partial Correlation Analysis Between Each Parameter and IHV of SIH Patients

Owing to considerably close correlation between each of the above parameters and age in the SIH patients, the partial correlation was analyzed in order to show further

dependability of the correlation analysis between values of SP, DP, TCH, TG, HDL-CH, LDL-CH, EM-CH, BMI, DCSC, DPAC and IHV of SIH patients. The findings showed that with increased SP, DP, LDL-CH, BMI, DCSC and DPAC as well as decreased HDL-CH and EM-CH, IHV of the SIH patients were increased gradually (Table 3).

TABLE 3

Partial Correlation Analysis Between Each Parameter and IHV

Correlative Items	*n*	Controlling Factor	Partial Correlation Coefficient	*P*
SP With IHV	500	Age	0.7198	<0.0001
DP With IHV	500	Age	0.4847	<0.0001
TCH With IHV	500	Age	– 0.0804	0.0731
TG With IHV	500	Age	0.0838	0.0609
HDL-CH With IHV	500	Age	– 0.1343	0.0021
LDL-CH With IHV	500	Age	0.3702	<0.0001
EM-CH With IHV	500	Age	– 0.5477	<0.0001
BMI With IHV	500	Age	0.2153	<0.0001
DCSC With IHV	500	Age	0.1617	0.0004
DPAC With IHV	500	Age	0.2042	<0.0001

Linear Stepwise Regression Analysis Among Parameters and IHV in SIH Patients

The findings that the linear stepwise regression analysis, using 0.050 (the probability of *F*) as the stepping method criteria, for values of SP, DP, TCH, TG, HDL-CH, LDL-CH, EM-CH, BMI, DCSC, DPAC, age and IHV of the SIH patients suggested that $Y=-12.4583 + 0.1127_{SP} - 1.1977_{EM\text{-}CH} + 0.9788_{LDL\text{-}CH} + 0.2477_{BMI} + 0.0382_{DCSC} + 0.0248_{DP}$, and that the standardized regressive coefficients (beta) were 0.5001 ($P<0.0001$), –0.2825 ($P<0.0001$), 0.1895 ($P<0.0001$), 0.1232 ($P<0.0001$), 0.0769 ($P=0.0041$) and 0.0715 ($P=0.0462$), respectively, and that the partial correlative coefficients were 0.5064 ($P<0.0001$), –0.4019 ($P<0.0001$), 0.2936 ($P<0.0001$), 0.2035 ($P<0.0001$), 0.1289 ($P<0.0001$) and 0.0896 ($P=0.0073$), respectively.

DISCUSSION

It is well known that normal arterial pressure and its dynamic balance play important roles in human metabolism, human systems, organs, tissues and cells, and have close relations to human health. Both increased and decreased arterial pressure will cause, in all likelihood, many diseases, thus endangering human's lives[1-13]. Status of blood lipometabolism has close relations to human health, and cholesterol, as an amphipathic lipid, is an important component of cellular membranes, and is the parent molecule from which all other steroids in human bodies are synthesized, including major hormones such as adrenocortical and sex hormones, vitamin D, and bile acids. Additionally, cholesterol is also a main component that structures "skeleton" of cellular membranes, and plays an important role in keeping fluidity, viscoelasticity and deformability of erythrocytic membranes and other cellular membranes in human bodies[28-30]. High density lipoprotein is synthesized and

secreted from the liver, and it scavenges excessive cholesterol and triacylglycerols from other tissues and the blood stream, returning them to the liver where they are excreted[28-30]. Triacylglycerols and low density lipoprotein play important roles in human metabolism[28-30]. However, lipometabolism disorder may induce cerebrovascular diseases[1-4,10,11,13-17, 25-29]. It is beyond all doubt that cigarette smoking, heavy alcohol intake, obesity and aging may also induce cerebrovascular diseases[1-4,8,10,11,13,18-24,28-30].

The findings of the present study showed that significantly increased SP, DP, LDL-CH, BMI and DCSC, and significantly decreased EM-CH were, in all likelihood, the main factors affecting SIH and IHV in SIH patients. There might be several interpretations.

Increased SP and DP may form a stronger torrential flow (turbulent blood rushing) in arterial bloodstream, and produce shear stress and force (the force of turbulent blood rushing) on endothelium, and produce bigger pressure on the wall of arterial vessels, thereby increasing the fatalness of breaking in arterial vessels, enhancing the probability of occurrence of SIH[1-13]. LDL in bloodstream can be oxidized to oxidized-LDL. As a result of abnormally elevated shear stress, as occurs in arterial system with hypertension, vascular endothelial cells change their expression of adhesion molecules. The new adhesion molecules whose expression is induced are molecules that promote migration of monocytes to the subendothelial (intimal) space. There, under the influence of cytokines derived from either endothelium or T-cells, the monocytes differentiate into macrophages. Thus, subsequent to foam-cell formation, smooth muscle cells migrate toward the foam cells and are induced to proliferate and accumulate calcium. This results somehow in inflammatory ulceration of the fatty streak to form an atherosclerotic plaque. The higher the concentration of LDL in blood, the longer any given LDL molecule circulates before its removal. Blood is an oxidizing environment, hence the longer LDL circulates, the greater the fraction with which it will be oxidized[1-4,10,11,13-17]. Smoking increases the rate of LDL oxidation that would otherwise occur at any given serum LDL concentration and may also injure endothelium through carbon monoxide exposure, thereby triggering adhesion protein changes that initiate atherosclerosis[1-4, 8, 10, 11, 18-20]. Obesity, is an independent risk factor for atherosclerosis due to its association with hypercholesterolemia, hypertriglyceridemia, diabetes, and hypertension[1-4,19,20,22,24]. Therefore, significant elevation of the above parametric values may play important roles in SIH's occurrence and development, and also in forming and developing IHV in SIH patients. Additionally, decreased HDL fails to scavenge excessive TG and LDL-CH from bloodstream and other tissues, thus forming easily atherosclerosis[28], while decreased EM-CH may increase the fragility and rigidity of erythrocytic membrane and other cellular membranes like endothelial cell membranes, and may decrease fluidity, viscoelasticity and deformability of erythrocytic membrane and other cellular membranes like endothelial cell membranes, thereby increasing further the risk of SIH[28], and affecting IHV in SIH patients.

The findings of the present study showed that both SP and DP were significantly related to risk of SIH stroke and IHV in cases of SIH stroke, and that both linear correlation and partial correlation were stronger for SP than DP. These findings emphasized the importance of SP, as opposed to DP, as a risk factor for SIH stroke and IHV in cases of SIH stroke.

In conclusion, the findings of the present study suggest that increased arterial systolic and diastolic pressures and decreased erythrocytic membrane cholesterol are the strongest and most consistent factors affecting spontaneous intracerebral hemorrhage and intracerebral hemorrhagic volumes, and that other correlative factors are low density lipoprotein, body mass index and daily cigarette smoking consumption. Therefore, it is necessary for all to keep normal blood pressures, maintain intake of normal lipids, manage normal body weight and abstain from cigarette smoking and heavy alcohol drinking[1-22, 24, 28-30].

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